2-sided

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 311/29, 311/46, C07D 295/22, A61K 31/18, 31/445, 31/41

A1

(11) International Publication Number: WO 99/62873

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/GB99/01735

(22) International Filing Date: 2 June 1999 (02.06.99)

(30) Priority Data:
9811932.4 4 June 1998 (04.06.98) GB

(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

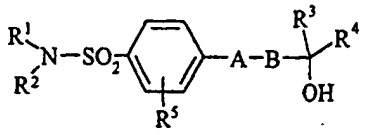
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BUTLIN, Roger, John [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). BURROWS, Jeremy, Nicholas [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BILL, Kevin; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BENZENESULPHONAMIDE DERIVATIVES AS PYRUVATE DEHYDROGENASE ACTIVATORS



(I)

(57) Abstract

The use of a compound of formula (I) wherein: either R^1 and R^2 are each selected independently from hydrogen, C_{1-3}alkyl, pyridyl and optionally substituted phenyl or together with the nitrogen atom to which they are attached form a ring; A–B is selected from NHCO, OCH_2, SCH_2, $NHCH_2$, *trans*–vinylene and ethynylene; R^3 and R^4 are independently C_{1-3}alkyl optionally substituted fluoro and chloro or together form a ring optionally substituted with fluoro; and R^5 is hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano, nitro, C_{2-4}alkenyloxy or trifluoromethylthio; in the manufacture of a medicament for use in the elevation of PDH activity in warm–blooded animals such as humans is described. Salts and esters of compounds of formula (I) are also described.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

BENZENESULPHONAMIDE DERIVATIVES AS PYRUVATE DEHYDROGENASE ACTIVATORS

The present invention relates to compounds which elevate pyruvate dehydrogenase (PDH) activity, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with reduced PDH activity, to their use as medicaments and to their use in the manufacture of medicaments for use in the elevation of PDH activity in warm-blooded animals such as humans.

Within tissues adenosine triphosphate (ATP) provides the energy for synthesis of complex molecules and, in muscle, for contraction. ATP is generated from the breakdown of energy-rich substrates such as glucose or long chain free fatty acids. In oxidative tissues such as muscle the majority of the ATP is generated from acetyl CoA which enters the citric acid cycle, thus the supply of acetyl CoA is a critical determinant of ATP production in oxidative tissues. Acetyl CoA is produced either by β-oxidation of fatty acids or as a result of glucose metabolism by the glycolytic pathway. The key regulatory enzyme in controlling the rate of acetyl CoA formation from glucose is PDH which catalyses the oxidation of pyruvate to acetyl CoA and carbon dioxide with concomitant reduction of nicotinamide adenine dinucleotide (NAD) to NADH.

In disease states such as both non-insulin dependent (NIDDM) and insulin-dependent diabetes mellitus (IDDM), oxidation of lipids is increased with a concomitant reduction in utilisation of glucose, which contributes to the hyperglycaemia. Reduced glucose utilisation in both IDDM and NIDDM is associated with a reduction in PDH activity. In addition, a further consequence of reduced PDH activity may be that an increase in pyruvate concentration results in increased availability of lactate as a substrate for hepatic gluconeogenesis. It is reasonable to expect that increasing the activity of PDH could increase the rate of glucose oxidation and hence overall glucose utilisation, in addition to reducing hepatic glucose output. Another factor contributing to diabetes mellitus is impaired insulin secretion, which has been shown to be associated with reduced PDH activity in pancreatic β-cells (in a rodent genetic model of diabetes mellitus Zhou et al. (1996) Diabetes 45: 580-586).

Oxidation of glucose is capable of yielding more molecules of ATP per mole of oxygen than is oxidation of fatty acids. In conditions where energy demand may exceed energy supply, such as myocardial ischaemia, intermittent claudication, cerebral ischaemia and reperfusion,

(Zaidan et al., 1998; J. Neurochem. 70: 233-241), shifting the balance of substrate utilisation in favour of glucose metabolism by elevating PDH activity may be expected to improve the ability to maintain ATP levels and hence function.

An agent which is capable of elevating PDH activity may also be expected to be of benefit in treating conditions where an excess of circulating lactic acid is manifest such as in certain cases of sepsis.

The agent dichloroacetic acid (DCA) which increases the activity of PDH after acute administration in animals, (Vary et al., 1988; Circ. Shock, 24: 3-18), has been shown to have the predicted effects in reducing glycaemia, (Stacpoole et al., 1978; N. Engl. J. Med. 298: 526-530), and as a therapy for myocardial ischaemia (Bersin and Stacpoole 1997; American Heart Journal, 134: 841-855) and lactic acidaemia, (Stacpoole et al., 1983; N. Engl. J. Med. 309: 390-396).

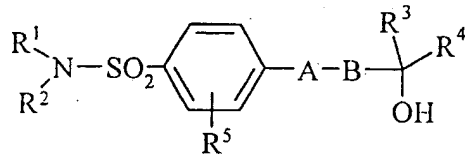
PDH is an intramitochondrial multienzyme complex consisting of multiple copies of several subunits including three enzyme activities E1, E2 and E3, required for the completion of the conversion of pyruvate to acetyl CoA (Patel and Roche 1990; FASEB J., 4: 3224-3233). E1 catalyses the non-reversible removal of CO_2 from pyruvate; E2 forms acetyl CoA and E3 reduces NAD to NADH. Two additional enzyme activities are associated with the complex: a specific kinase which is capable of phosphorylating E1 at three serine residues and a loosely-associated specific phosphatase which reverses the phosphorylation. Phosphorylation of a single one of the three serine residues renders the E1 inactive. The proportion of the PDH in its active (dephosphorylated) state is determined by a balance between the activity of the kinase and phosphatase. The activity of the kinase may be regulated in vivo by the relative concentrations of metabolic substrates such as NAD/NADH, CoA/acetylCoA and adenine diphosphate (ADP)/ATP as well as by the availability of pyruvate itself.

European Patent Publication No. 625516 refers to compounds which are capable of relaxing bladder smooth muscle and which may be used in the treatment of urge incontinence. We have found, surprisingly, that compounds also containing a sulphonamide moiety disclosed in the present invention are very good at elevating PDH activity, a property nowhere disclosed in EP 625516.

The present invention is based on the surprising discovery that certain compounds elevate PDH activity, a property of value in the treatment of disease states associated with disorders of

glucose utilisation such as diabetes mellitus, obesity, (Curto et al., 1997; Int. J. Obes. 21: 1137-1142), and lactic acidaemia. Additionally the compounds may be expected to have utility in diseases where supply of energy-rich substrates to tissues is limiting such as peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, muscle weakness, hyperlipidaemias and atherosclerosis (Stacpoole et al., 1978; N. Engl. J. Med. 298: 526-530). A compound that activates PDH may also be useful in treating Alzheimer disease (AD) (J Neural Transm (1998) 105: 855-870).

According to one aspect of the present invention there is provided the use of a compound of the formula **(I)**:



(I)

wherein:

either $\mathbf{R^1}$ and $\mathbf{R^2}$ are each selected independently from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is unsubstituted or substituted by one or two substituents selected independently from C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, hydroxy, halo and cyano,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl, pyrrolidinyl or imidazolyl;

A-B is selected from NHCO, OCH_2, SCH_2, $NHCH_2$, *trans*-vinylene and ethynylene;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are independently C_{1-3}alkyl substituted by from 0 to 2k+1 atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said C_{1-3}alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4, together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to 2m-2 fluorine atoms wherein m is the number of carbon atoms in said ring; and

$\mathbf{R^5}$ is hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano, nitro, C_{2-4}alkenyloxy or trifluoromethylthio;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-4}alkyl" includes propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "C_{1-4}haloalkoxy" includes 1-chloroethoxy and 2-fluoroethoxy and "C_{1-4}haloalkyl" includes 1-bromopropyl, 2-iodopropylyl and trifluoromethyl. The term "halo" refers to fluoro, chloro, bromo and iodo. Examples of "C_{1-4}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{2-4}alkenyloxy" are vinyloxy and allyloxy.

Preferred values for R^1, R^2, R^3, R^4, R^5, X and A-B are as follows.

Preferably R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is optionally substituted by one or two substituents selected from halo, C_{1-4}alkoxy, C_{1-4}alkyl, hydroxy and cyano,

or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

More preferably R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is optionally substituted by one or two substituents selected from methoxy, hydroxy, C_{1-4}alkyl and cyano,

or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

In another aspect of the invention more preferably R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl and phenyl which is optionally substituted by one or two substituents selected from methoxy, methyl and halo,

or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

Particularly R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl and unsubstituted phenyl,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

In another aspect of the invention particularly R^1 and R^2 are each independently selected from hydrogen, methyl, ethyl, propyl, phenyl,4-methoxyphenyl and 2-chloro-5-methylphenyl,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

Preferred combinations of R^1 and R^2 are as follows.

Preferably R^1 and R^2 are both hydrogen, methyl, ethyl or propyl or one of R^1 and R^2 is hydrogen or methyl and the other is phenyl, or R^1 and R^2 together with the nitrogen to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

In another aspect of the invention, more preferably R^1 and R^2 are both hydrogen, methyl, ethyl or propyl or one of R^1 and R^2 is hydrogen, methyl, ethyl or phenyl and the other is phenyl, which is optionally substituted by one or two substituents selected from methoxy, methyl and halo, or R^1 and R^2 together with the nitrogen to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

Preferably R^3 and R^4 are independently C_{1-3}alkyl substituted by 0 to 2k+1 atoms selected from fluoro and chloro, wherein k is the number of carbon atoms in the said C_{1-3}alkyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

More preferably R^3 and R^4 are independently C_{1-2}alkyl substituted by 0 to 2k+1 atoms selected from fluoro and chloro, wherein k is the number of carbon atoms in the said C_{1-2}alkyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

Particularly R^3 and R^4 are independently methyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and perfluoroethyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

More particularly R^3 and R^4 are independently methyl, fluoromethyl, difluoromethyl and trifluoromethyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

Preferred combinations of R^3 and R^4 are as follows.

Preferably one of R^3 and R^4 is methyl and the other is trifluoromethyl.

Where applicable, the R-configuration generally represents a preferred stereochemistry for compounds of formula **(I)**.

Preferably R^5 is selected from nitro, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy and hydrogen.

More preferably R^5 is selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, nitro and hydrogen.

Particularly R^5 is selected from methyl, methoxy and hydrogen.

More particularly R^5 is hydrogen.

In another aspect of the invention preferably R^5 is hydrogen or methyl.

In a further aspect of the invention preferably R^5 is methyl.

In one aspect of the invention preferably R^5 is as hereinbefore defined except hydrogen, that is it is preferable that R^5 is not hydrogen.

Preferably A-B is selected from -NHC(O)-, trans-vinylene and ethynylene.

More preferably A-B is -NHC(O)-.

According to another aspect of the present invention there is provided the use of a compound of formula **(I)** wherein:

R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is optionally substituted by one or two substituents selected from halo, C_{1-4}alkoxy, C_{1-4}alkyl, hydroxy and cyano,

or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl;

R^3 and R^4 are independently C_{1-3}alkyl substituted by 0 to 2k+1 atoms selected from fluoro and chloro, wherein k is the number of carbon atoms in the said C_{1-3}alkyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms;

R^5 is nitro, C_{1-4}alkyl, C_{1-4}alkoxy or hydrogen;

A-B is -NHC(O)-, trans-vinylene or ethynylene;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

According to a further preferred aspect of the present invention there is provided the use of a compound of formula **(I)** wherein:

R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl, pyridyl and unsubstituted phenyl,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

R^3 and R^4 are independently methyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and perfluoroethyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms;

R^5 is from methyl, methoxy or hydrogen;

A-B is -NHC(O)-;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

According to a particularly preferred aspect of the present invention there is provided the use of a compound of formula **(I)** wherein:

R^1 and R^2 are both hydrogen, methyl, ethyl or propyl or one of R^1 and R^2 is hydrogen or methyl and the other is phenyl, or R^1 and R^2 together with the nitrogen to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl;

one of R^3 and R^4 is methyl and the other is trifluoromethyl;

R^5 is hydrogen;

A-B is -NHC(O)-;

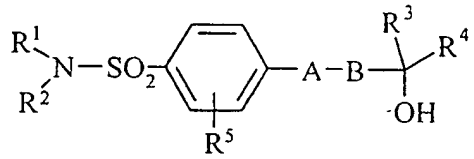
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

According to another aspect of the present invention there is provided the use of a compound which comprises a compound as set out in the Examples (and in particular Examples 1-11) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

Where applicable, the R-configuration generally represents a preferred stereochemistry for compounds of formula **(I)**.

Many of the compounds of the present invention are novel and as such are provided as a further feature of the present invention.

According to another aspect of the present invention there is provided a compound of the formula **(I)**:



(I)

wherein ring R^1, R^2, R^3, R^4, R^5 and A-B are as defined hereinbefore,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof provided said compound is not:

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-piperidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-pyrrolidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholino-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholinosulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl] propanamide;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinyl-sulphonyl)phenyl]but-1-yne;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinyl-sulphonyl)phenyl]-trans-but-1-ene;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-methyl-*N*-phenylaminosulphonyl)phenyl]but-1-yne;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-Methyl-*N*-phenylaminosulphonyl)phenyl]-trans-but-1-ene;

1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methylbut-1-yne;

1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methyl-trans-but-1-ene;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylamino-sulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-diphenylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide; or

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(morpholino-sulphonyl)phenyl]-trans-but-1-ene;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

According to another aspect of the present invention there is provided a compound of formula **(I)** wherein:

R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is optionally substituted by one or two substituents selected from halo, C_{1-4}alkoxy, C_{1-4}alkyl, hydroxy and cyano,

or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl;

R^3 and R^4 are independently C_{1-3}alkyl substituted by 0 to 2k+1 atoms selected from fluoro and chloro, wherein k is the number of carbon atoms in the said C_{1-3}alkyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms;

R^5 is nitro, C_{1-4}alkyl, C_{1-4}alkoxy or hydrogen;

A-B is -NHC(O)-, trans-vinylene or ethynylene;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, provided said compound is not:

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-piperidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-pyrrolidinyl-sulphonyl)phenyl]propanamide;
3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholino-sulphonyl)phenyl]propanamide;
3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholinosulphonyl)phenyl]propanamide;
N-[4-(*N*,*N*-dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide;
N-[4-(*N*,*N*-dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;
N-[4-(aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;
N-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;
3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl]
propanamide;
4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinyl-sulphonyl)phenyl]but-1-yne;
4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinyl-sulphonyl)phenyl]-trans-but-1-ene;
4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-methyl-*N*-phenylaminosulphonyl)phenyl]but-1-yne;
4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-Methyl-*N*-phenylaminosulphonyl)phenyl]
-trans-but-1-ene;
1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methylbut-1-yne;
1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methyl-trans-but-1-ene;
3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylamino-sulphonyl)phenyl]propanamide;
N-[4-(*N*,*N*-diphenylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide; or
4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(morpholino-sulphonyl)phenyl]-trans-but-1-ene;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

According to a further preferred aspect of the present invention there is provided a compound of formula **(I)** wherein:

R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl pyridyl and unsubstituted phenyl,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

R^3 and R^4 are independently methyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and perfluoroethyl,

or R^3 and R^4, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms;

R^5 is methyl, methoxy or hydrogen;

A-B is -NHC(O)-;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, provided said compound is not

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-piperidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-pyrrolidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholino-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholinosulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl] propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylamino-sulphonyl)phenyl]propanamide; or

N-[4-(*N*,*N*-diphenylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

According to a particularly preferred aspect of the present invention there is provided a compound of formula **(I)** wherein:

R^1 and R^2 are both hydrogen, methyl, ethyl or propyl or one of R^1 and R^2 is hydrogen or methyl and the other is phenyl, or R^1 and R^2 together with the nitrogen to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl;

one of R^3 and R^4 is methyl and the other is trifluoromethyl;

R^5 is hydrogen;

A-B is -NHC(O)-;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, provided said compound is not:

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-piperidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-pyrrolidinyl-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholino-sulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholinosulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

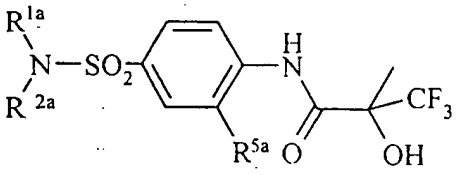
N-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl]propanamide; or

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylamino-sulphonyl)phenyl]propanamide;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

According to a further feature of the invention there is provided a compound of the formula **(I')**:



(I')

wherein:

R^{1a} and R^{2a} are each selected independently from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is unsubstituted or substituted by one or two substituents selected independently from C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, hydroxy, halo and cyano,

or R^{1a} and R^{2a} together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl, pyrrolidinyl or imidazolyl; and

R^{5a} is C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano, nitro, C_{2-4}alkenyloxy or trifluoromethylthio;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferably R^{1a} and R^{2a} are each selected independently from hydrogen, C_{1-3}alkyl and phenyl which is unsubstituted or substituted by one substituent selected independently from C_{1-4}alkyl, C_{1-4}alkoxy and halo,

or R^{1a} and R^{2a} together with the nitrogen atom to which they are attached form morpholino.

More preferably R^{1a} and R^{2a} are each selected independently from hydrogen, methyl, ethyl, phenyl, 2-chloro-5-methylphenyl and 4-methoxyphenyl,

or R^{1a} and R^{2a} together with the nitrogen atom to which they are attached form morpholino.

Preferably R^{5a} is methyl or methoxy.

More preferably R^{5a} is methyl.

Where applicable, the R-configuration generally represents a preferred stereochemistry for compounds of formula **(I)**.

In another aspect of the invention, preferred compounds of the invention are any one of Examples 12-16 and pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof.

Preferred aspects of the invention are those that relate to the compound of formula **(I)** or **(I')** and pharmaceutically acceptable salts thereof.

Within the present invention it is to be understood that a compound of the formula **(I)** or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which elevates PDH activity and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated by those skilled in the art that certain compounds of formula **(I)** contain one or more asymmetrically substituted carbon and/or sulphur atoms, and accordingly may exist in, and be isolated as enantiomerically pure, a mixture of diastereoisomers or as a racemate. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, enantiomerically pure, mixture of diastereoisomers, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the elevation of PDH activity, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallisation

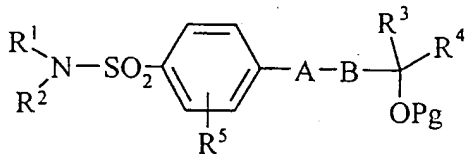
techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, (for example WO 9738124), by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the elevation of PDH activity by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula **(I)** and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which elevate PDH activity.

A compound of the formula **(I)**, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications, Publication Nos. 0524781, 0617010, 0625516, and in GB 2278054, WO 9323358 and WO 9738124.

Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (in which variable groups are as defined for formula **(I)** unless otherwise stated) comprises of:

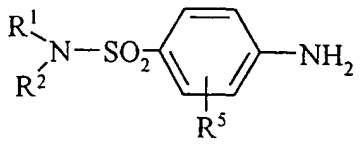
(a) deprotecting a protected compound of formula **(II)**



(II)

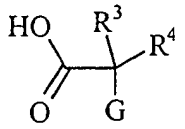
where Pg is an alcohol protecting group;

(b) for a compound of formula **(I)** in which A-B is -NHC(O)-, by coupling an aniline of formula **(III)**:



(III)

with an acid of formula **(IV)**:

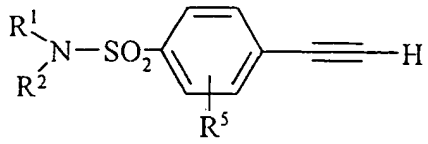


(IV)

wherein G is a hydroxyl group;

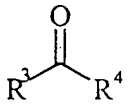
(c) by coupling an aniline of formula **(III)** with an activated acid derivative of formula **(IV)**;

(d) for a compound of formula **(I)** in which A-B is ethynylene, by reacting a corresponding alkyne of formula **(V)**:



(V)

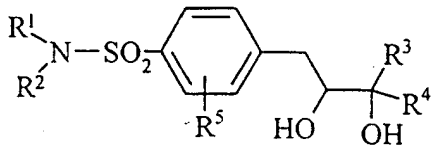
with a base, followed by treatment with a ketone of formula **(VI)**:



(VI);

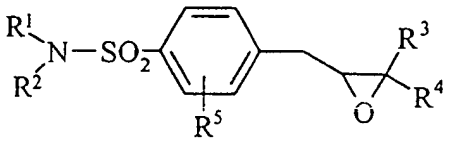
(e) for a compound of formula **(I)** in which A-B is *trans*-vinylene, by reducing a corresponding compound of formula **(I)** in which A-B is ethynylene with a reducing agent;

(f) for a compound of formula **(I)** in which A-B is *trans*-vinylene, by dehydration of a diol of formula **(VII)**:



(VII);

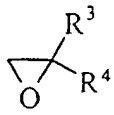
(g) for a compound of formula **(I)** in which A-B is *trans*-vinylene, by base catalysed opening of an epoxide of formula **(VIII)**:



(VIII);

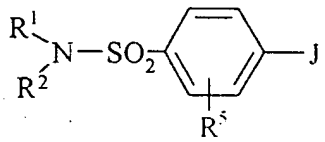
(h) for a compound of formula **(I)** in which A-B is $-NHCH_2-$, by reducing a corresponding compound of formula **(I)** in which A-B is -NHC(O)- with a reducing agent;

(i) for a compound of formula **(I)** in which A-B is $-OCH_2-$, $-SCH_2-$ or $-NHCH_2-$ by reacting an ethylene oxide of formula **(IX)**:



(IX)

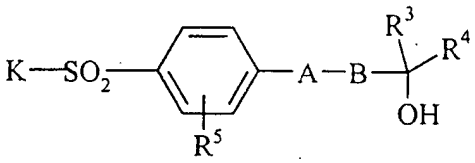
with a corresponding compound of formula **(III)** or a compound of formula **(X)**:



(X)

where J is -OH or -SH;

(j) by reacting a compound of formula **(XI)**:



(XI)

where K is a leaving atom or group and in which A-B is OCH_2, SCH_2 or $NHCH_2$ or -NHC(O)-, with an amine of formula R^1R^2NH;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* cleavable ester.

K is a leaving atom or group, suitable values for K are, for example, a halogen atom such as fluoro or chloro.

Specific conditions for the above reactions are as follows:

(a) suitable protecting groups include a benzyl group, a silyl group or an acetyl protecting group. Examples of suitable reagents for deprotecting an alcohol of formula **(II)** are:

1) when Pg is benzyl:

(i) hydrogen in the presence of palladium/carbon catalyst, i.e. hydrogenolysis; or

(ii) hydrogen bromide or hydrogen iodide;

2) when Pg is a silyl protecting group:

(i) tetrabutylammonium fluoride; or

(ii) aqueous hydrofluoric acid;

3) when Pg is acetyl:

i) mild aqueous base for example lithium hydroxide.

The reaction can be conducted in a suitable solvent such as ethanol, methanol, acetonitrile, or dimethylsulphoxide and may conveniently be performed at a temperature in the range of -40 to 100°C.

(b) The reaction can be conducted in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, for example thionyl chloride (or oxalyl chloride), carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

(c) Suitable activated acid derivatives include for example acid chlorides, acid anhydrides, or phenyl esters, wherein G is a hydroxyl group which may be suitably protected as a stable ester or ether. This coupling may be achieved optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in

the range of -40 to 40°C.

(d) Suitable bases include lithium diisopropylamide (LDA), *n*-butyllithium or *tert*-butyllithium. The reaction may be performed at a temperature in the range of -100 to -40°C preferably at a temperature in the range of -70 to -40°C and in a solvent such as tetrahydrofuran, diethyl ether, or 1,2-dimethoxyethane.

(e) Suitable reducing agents are for example lithium aluminium hydride or sodium bis(methoxyethoxy)aluminium hydride. The reaction can be conducted in a suitable solvent such as tetrahydrofuran or diethyl ether, and at a temperature in the range of 0 to 50°C.

(f) This reaction is conveniently performed in the presence of an acid catalyst (for example *p*-toluenesulphonic acid), neat or with a solvent such as toluene or dichloromethane at a temperature in the range of 0 to 200 °C preferably a temperature in the range of 20 to 100 °C.

(g) The opening may be carried out in a suitable organic solvent for example, ethers or toluene. Ethers such as tetrahydrofuran are preferred. Suitable bases include potassium *tert*-butoxide or sodium hydride. The opening may be carried out at a temperature in the range of -50 to 100°C, preferably at a temperature in the range of 0 to 50 °C for example room temperature.

(h) Suitable reducing agents are lithium aluminium hydride or borane. The reaction can conveniently be carried out at a temperature in the range of 0°C to reflux, in solvents such as for example diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane.

(i) This reaction is conveniently performed in the presence of a base for example sodium hydride or triethylamine. The reaction can be conducted at reflux in a solvent such as dichloromethane, tetrahydrofuran, or diethyl ether.

(j) The reaction is conveniently performed in the presence of a base, for example a tertiary amine such as triethylamine and in the presence of a catalyst for example dimethylaminopyridine. Suitable solvents for the reaction include nitriles such as acetonitrile and amides such as dimethylformamide. The reaction is conveniently performed at a temperature in the range of from 0 to 120°C.

If not commercially available, the necessary starting materials for the procedures such as that described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the

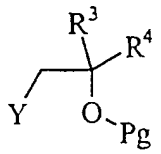
procedures described in the examples.

For example, it will be appreciated that certain of the optional aromatic substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acylhalide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by, for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl using, for example, hydrogen peroxide in acetic acid with heating or 3-chloroperbenzoic acid.

Specific examples of the techniques used to make that starting materials described above are illustrated, but not limited by, the following examples in which variable groups are as defined for formula **(I)** unless otherwise stated.

1) Preparation of compounds of formula **(II)**.

a) compounds of formula **(II)** in which A-B is OCH_2, SCH_2 or $NHCH_2$ may be made by treating the corresponding compound of formula **(X)** wherein J is -OH, -SH or a compound of formula **(III)** with a compound of formula **(XII)**:

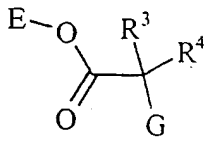


(XII)

where Y is a leaving group for example mesylate; in the presence of a base such as an alkali metal hydride (e.g. sodium hydride), in a solvent such as tetrahydrofuran, *N*,*N*-dimethylformamide, dimethyl sulphoxide, or 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, and at a temperature of 20°C to reflux.

b) A compound of formula **(II)**, wherein A-B is -NHC(O)-, may be made by coupling a compound of formula **(III)** with a compound of formula **(IV)** (where G is hydroxy protected with a protecting group) in a manner analogous to that described for procedure (b) of preparations of a compound of formula **(I)** above.

Compounds of formula **(IV)** where G is hydroxy protected with a protecting group may be made by conventional procedures. For example, cleavage of the ester group of a compound of formula **(XIII)**:



(XIII)

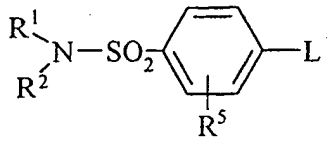
where E is a carboxy protecting group (e.g. Me);

under standard conditions such as mild alkaline conditions, for example, aqueous lithium hydroxide.

Compounds of formula **(XIII)** where G is protected hydroxy are prepared by protecting a compound of formula **(XIII)** where G is hydroxy by reaction with a compound such as benzyl chloride or benzyl bromide (in the presence of a suitable base such as sodium hydride and optionally with a catalyst such as sodium iodide, to provide a benzyl protecting group) or any of the conventional silylating agents known and used for such purpose (for example 2-trimethylsilylethoxymethyl chloride, in the presence of a suitable base such as triethylamine optionally in the presence of a catalyst such as dimethylaminopyridine).

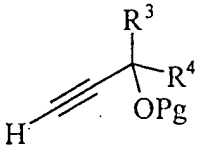
Compounds of formula **(XIII)** where G is hydroxy are prepared by esterifying an acid of formula **(IV)** by a conventional esterification procedure such as reaction with a C_{1-6}alcohol (e.g. methanol) in the presence of an acid catalyst (for example sulphuric acid).

c) A compound of formula **(II)**, wherein A-B is ethynylene, may be made by reacting a compound of formula **(XIV)**:



(XIV)

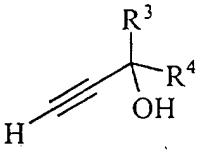
wherein L is a leaving group such as bromo, iodo, or triflate, with an acetylene of formula (XV)



(XV)

in the presence of a catalyst such as a combination of copper (I) iodide and bis(triphenylphosphine)palladium dichloride or palladium (II) acetate. The reaction can be conducted in an inert solvent such as tetrahydrofuran, benzene, or toluene, or in a basic solvent such as diethylamine or triethylamine, and at a temperature in the range of -20 to 110°C.

A compound of formula (XV) may be made by reacting a compound of formula (XVI)



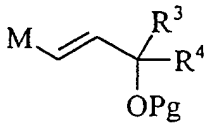
(XVI)

with an agent such as:

i) benzyl bromide (to provide a benzyl protecting group), this reaction may conveniently be conducted in the presence of a base such as sodium hydride and optionally in the presence of a catalyst such as sodium iodide in a solvent such as tetrahydrofuran at a temperature of about -78 to about 100 °C; or

ii) any of the conventional silylating agents known and used for such purpose (such as for example *tert*-butyl dimethylsilylchloride or triflate, in the presence of a suitable base such as 1,8-Diazabicyclo[5.4.0]undec-7-ene or triethylamine optionally in the presence of a catalyst such as dimethylaminopyridine) at a temperature of about -78 to about 100 °C.

d) A compound of formula **(II)**, wherein A-B is *trans*-vinylene, may be made by reacting a compound of formula **(XVII)**:



(XVII)

where M is an alkylmetal group such as a trialkyltin (for example tributyl- or trimethyl-tin) or a bisalkyloxyborane (for example catecholborane);

with a compound of formula **(X)**, wherein J may be a leaving group for example iodide, bromide or triflate in the presence of a catalyst such as bis(triphenylphosphine)palladium dichloride or tetrakis(triphenylphosphine)palladium (0). The reaction may conveniently be conducted in a suitable inert solvent such as a tetrahydrofuran or dimethylformamide at a temperature of 0 - 150°C.

A compound of formula **(XVII)** may be made by a reaction of a compound of formula **(XV)**

i) with an agent such as catecholborane, to form the vinylborane compound; or

ii) a trialkyltinhydride in the presence of a catalytic amount of a radical chain initiator such as, for example, aza-*bis*-isobutyronitrile or by using trialkyltinhydride pre-treated with a strong base (such as an alkyllithium) and copper (I) cyanide, or by using a transition metal catalyst such as, for example, tetrakis(triphenylphosphine)palladium(0) to form a compound of formula **(XVII)** where M is trialkyltin.

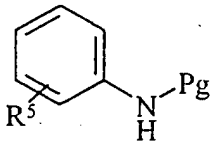
These reactions may conveniently be conducted in a suitable inert solvent such as tetrahydrofuran, toluene or xylene at a temperature of from 0 - 150°C.

Compounds of formula **(XVI)** may be made by reacting a compound of formula **(VI)** with an alkali metal acetylide (for example lithium acetylide) or alkaline earth metal acetylide (for example magnesium acetylide). The reaction may be conducted in a solvent such as tetrahydrofuran, diethyl ether, or 1,2-dimethoxyethane and at a temperature of -100 to 25 °C.

2) Preparation of compounds of formula **(III)**.

A compound of formula **(III)** may be prepared:

i) from a compound of formula **(XVIII)**



(XVIII)

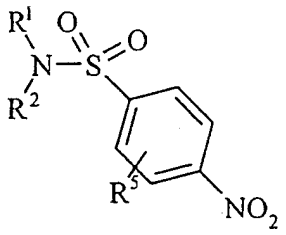
wherein Pg is a protective group such as for example acetyl;

a) by treatment with chlorosulphonic acid under standard conditions, and then

b) formation of the sulphonamide under standard conditions as described above in process (j) for preparation of a compound of formula **(I)** and then

c) cleavage of the protecting group under mild alkaline conditions (for example when Pg is acetyl with a base such as aqueous sodium hydroxide); or

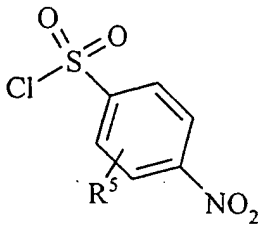
ii) by reducing a compound of formula **(XIX)**:



(XIX)

under standard conditions for example by a reducing agent such as tin (II) chloride or iron dust in conjunction with concentrated acid to give a compound of formula **(III)**.

A compound of formula **(XIX)** may be made by reacting a compound of formula **(XX)**:

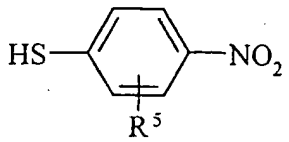


(XX)

with an amine of formula R^1R^2NH- in a procedure analogous to that used in process (j) for preparation of a compound of formula **(I)** above.

A compound of formula **(XX)** may be prepared:

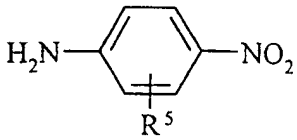
a) by oxidising a compound of formula **(XXI)**:



(XXI)

under standard conditions for example with chlorine in a suitable solvent such as acetic acid at a temperature of -78 to about 100°C; or

b) by diazotizing a compound of formula (XXII):



(XXII)

under standard conditions for example with nitrous acid and sulphuric acid followed by reaction with a mixture of sulphur dioxide and copper (II) chloride in a suitable solvent such as water or a water/acetic acid solution.

3) Resolution of compounds of formula (IV)

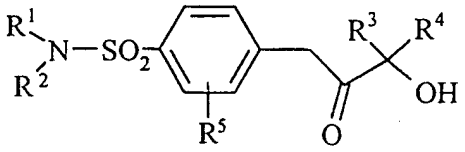
If the resolved acid is required it may be prepared by any of the known methods for preparation of optically-active forms (for example, by recrystallisation of the chiral salt {for example WO 9738124}, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase). For example if an (R)-(+) resolved acid is required it may be prepared by the method of Scheme 2 in World Patent Application Publication No. WO 9738124 for preparation of the (S)-(-) acid, i.e. using the classical resolution method described in European Patent Application Publication No. EP 0524781, also for preparation of the (S)-(-) acid, except that (1S,2R)-norephedrine may be used in place of (S)-(-)-1-phenylethylamine.

4) Preparation of compounds of formula (V).

A compound of formula (V) may be prepared by reacting a compound of formula (XIV), wherein L is bromo, iodo or triflate with trimethylsilylacetylene in the presence of a catalyst such as a combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide in diethylamine or triethylamine, followed by treatment with a base (for example potassium carbonate) in a C_{1-6}alcohol (such as methanol) as the solvent to remove the trimethylsilyl group.

5) Preparation of compounds of formula **(VII)**.

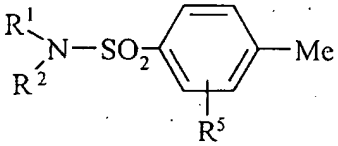
A compound of formula **(VII)** may be prepared from a compound of formula **(XXIII)**:



(XXIII)

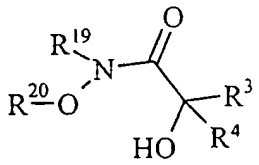
by reduction under standard conditions for example by using a hydride, such as sodium borohydride.

A compound of formula **(XXIII)** may be prepared by deprotonation of a compound of formula **(XXIV)**,



(XXIV)

with a strong base, for example lithium diisopropyl amide in an organic solvent, for example tetrahydrofuran at a temperature of -78 to 100 °C followed by addition of an amide of formula **(XXV)**:



(XXV)

in which R^{19} and R^{20} are each independently C_{1-6}alkyl or together with the atoms to which they are attached form a 5-7 membered ring.

An amide of formula **(XXV)** may be prepared from an acid of formula **(IV)**, or a reactive derivative thereof, by reaction with an amine of formula $R^{19}(R^{20}O)NH$ under standard conditions such as those described in process (b) for preparation of a compound of formula **(I)** above.

6) Preparation of compounds of formula **(VIII)**.

A compound of formula **(VIII)** may be prepared from a diol of formula **(VII)** using a

suitable dehydrating agent, for example bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenyl sulphur.

7) Preparation of compounds of formula **(IX)**.

A compound of formula **(IX)** may be made by treating a compound of formula **(VI)** with a trimethylsulphonium salt (such as trimethylsulphonium iodide) and a base (such as an alkali metal hydroxide) in a solvent such as dichloromethane.

8) Preparation of compounds of formula **(X)**.

a) A compound of formula **(X)** wherein J is -OH, may be prepared by diazotizing a compound of formula **(III)** under standard conditions such as those described above in 2(ii) above followed by heating the resulting compound in dilute sulphuric acid.

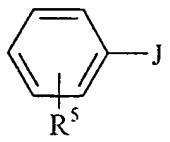
b) A compound of formula **(X)**, wherein J is -SH, may be prepared by reacting a compound of formula **(XIV)** where L is a leaving group (for example chloro) with an excess of methanethiol in the presence of sodium hydride.

9) Preparation of compounds of formula **(XI)**.

A compound of formula **(XI)** wherein K is chloro, in which A-B is OCH_2, SCH_2, $NHCH_2$ or -NHC(O)- may be prepared by

1) either

a) coupling a compound of formula **(XXVI)**



(XXVI)

wherein J is -OH, -SH or NH_2 with a compound of formula **(XII)** where Y is a leaving group for example mesylate; in the presence of a base such as an alkali metal hydride (e.g. sodium hydride), in a solvent such as tetrahydrofuran, *N*,*N*-dimethylformamide, dimethyl sulphoxide, or 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, and at a temperature of 20°C to reflux; or

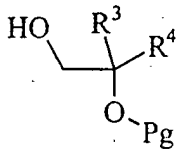
b) where A-B is -NHC(O)- coupling with a compound of formula **(XXVI)** where J is NH_2 with a compound of formula **(IV)**, following a method analogous to that of process (b) for preparation of a compound of formula **(I)** above.

Route a or b is then followed by:

2) treatment with chlorosulphonic acid.

10) Preparation of compounds of formula **(XII)**.

A compound of formula **(XII)**, wherein Y is mesylate may be prepared by reacting a compound of formula **(XXVII)**:



(XXVII)

with methanesulphonicacid chloride in the presence of a base such as triethylamine, in a solvent such as dichloromethane, and at a temperature of about -78 to 25°C.

Compounds of formula **(XXVII)** are prepared by reducing a compound of formula **(XIII)** with a suitable reducing agent such as lithium aluminium hydride in a solvent such as diethyl ether or THF and at a temperature of about 0 to about 25 °C.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature.

According to a further feature of the invention, there is provided a process for preparing a compound of formula **(I')** using any one of processes a), b), c) or j); and thereafter if necessary:

i) converting a compound of the formula **(I')** into another compound of the formula **(I')**;

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* cleavable ester.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

In cases where compounds of formula **(I)** are sufficiently basic or acidic to form stable acid or basic salts, administration of the compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following. Examples of suitable pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiologically acceptable anion, for example, tosylate, methanesulphonate, acetate, tartrate, citrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed such as sulphate, nitrate, and hydrochloride.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound of formula **(I)** (or its ester) with a suitable acid affording a physiologically acceptable anion. It is also possible with most compounds of the invention to make a corresponding alkali metal (e.g. sodium, potassium, or lithium) or alkaline earth metal (e.g. calcium) salt by treating a compound of formula **(I)** (and in some cases the ester) with a suitable base. For example by treatment with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g. the ethoxide or methoxide) in aqueous medium followed by conventional purification techniques.

In vivo cleavable esters of compounds of the invention may be made by coupling with a pharmaceutically acceptable carboxylic acid or an activated derivative thereof. For example, the coupling may be carried out by treating a compound of formula **(I)** with an appropriate acid chloride (for example, acetyl chloride, propionyl chloride, or benzoyl chloride) or acid anhydride (for example, acetic anhydride, propionic anhydride, or benzoic anhydride) in the presence of a suitable base such as triethylamine. Those skilled in the art will appreciate that other suitable carboxylic acids (including their activated derivatives) for the formation of *in vivo* cleavable esters are known to the art and these are also intended to be included within the scope of the invention. Catalysts such as 4-dimethylaminopyridine may also be usefully employed.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention.

The identification of compounds which elevate PDH activity is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In vitro elevation of PDH activity

This assay determines the ability of a test compound to elevate PDH activity. cDNA encoding PDH kinase may be obtained by Polymerase Chain Reaction (PCR) and subsequent cloning. This may be expressed in a suitable expression system to obtain polypeptide with PDH kinase activity. For example rat PDHkinaseII (rPDHKII) obtained by expression of recombinant protein in Escherichia coli (E. Coli), was found to display PDH kinase activity.

In the case of the rPDHKII (Genbank accession number U10357) a 1.3kb fragment encoding the protein was isolated by PCR from rat liver cDNA and cloned into a vector (for example pQE32 - Quiagen Ltd.). The recombinant construct was transformed into E. coli (for example M15pRep4 - Quiagen Ltd.). Recombinant clones were identified, plasmid DNA was isolated and subjected to DNA sequence analysis. One clone which had the expected nucleic acid sequence was selected for the expression work. Details of the methods for the assembly of recombinant DNA molecules and the expression of recombinant proteins in bacterial systems can be found in standard texts for example Sambrook et al, 1989, Molecular Cloning - A Laboratory Manual , 2nd edition, Cold Spring Harbour Laboratory Press. Other known PDH kinases for use in assays, may be cloned and expressed in a similar manner.

For expression of rPDHKII activity, E. coli strain M15pRep4 cells were transformed with the pQE32 vector containing rPDHKII cDNA. This vector incorporates a 6-His tag onto the protein at its N-terminus. E. coli were grown to an optical density of 0.6 (600 nM) and protein expression was induced by the addition of 10 μM isopropylthio-β-galactosidase. Cells were grown for 18 hours at 18°C and harvested by centrifugation. The resuspended cell paste was lysed by homogenisation and insoluble material removed by centrifugation at 24000xg for 1 hour. The 6-His tagged protein was removed from the supernatant using a nickel chelating nitrilotriacetic acid resin (Ni-NTA: Quiagen Ltd.) matrix (Quiagen) which was washed with 20 mM tris(hydroxymethyl)aminomethane-hydrogen chloride, 20 mM imidazole, 0.5 M sodium chloride pH 8.0, prior to elution of bound protein using a buffer containing 20 mM tris(hydroxymethyl)aminomethane-hydrogen chloride, 200 mM imidazole, 0.15 M sodium

chloride pH 8.0. Eluted fractions containing 6-His protein were pooled and stored in aliquots at -80°C in 10% glycerol.

Each new batch of stock enzyme was titrated in the assay to determine a concentration giving approximately 90% inhibition of PDH in the conditions of the assay. For a typical batch, stock enzyme was diluted to 7.5μg/ml.

For assay of the activity of novel compounds, compounds were diluted with 10% dimethylsulphoxide (DMSO) and 10μl transferred to individual wells of 96-well assay plates. Control wells contained 20μl 10% DMSO instead of compound. 40μl Buffer containing 50mM potassium phosphate buffer pH 7.0, 10mM ethylene glycol-bis(β-aminoethyl ether)-N,N,N,N-tetracetic acid (EGTA), 1mM benzamidine, 1mM phenylmethylsulphonyl fluoride (PMSF), 0.3mM tosyl-L-lysine chloromethyl ketone (TLCK), 2mM dithiothreitol (DTT), recombinant rPDHKII and compounds were incubated in the presence of PDH kinase at room temperature for 45 minutes. In order to determine the maximum rate of the PDH reaction a second series of control wells were included containing 10% DMSO instead of compound and omitting rPDHKII. PDH kinase activity was then initiated by the addition of 5 μM ATP, 2 mM magnesium chloride and 0.04 U/ml PDH (porcine heart PDH Sigma P7032) in a total volume of 50 μl and plates incubated at ambient temperature for a further 45 minutes. The residual activity of the PDH was then determined by the addition of substrates (2.5mM coenzyme A, 2.5mM thiamine pyrophosphate (cocarboxylase), 2.5mM sodium pyruvate, 6mM NAD in a total volume of 80μl and the plates incubated for 90 minutes at ambient temperature. The production of reduced NAD (NADH) was established by measured optical density at 340nm using a plate reading spectrophotometer. The ED_{50} for a test compound was determined in the usual way using results from 12 concentrations of the compound.

(b) <u>In vitro elevation of PDH activity in isolated primary cells</u>

This assay determines the ability of compounds to stimulate pyruvate oxidation in primary rat hepatocytes.

Hepatocytes were isolated by the two-step collagenase digestion procedure described by Seglen (Methods Cell Biol. (1976) 13, 29-33) and plated out in 6-well culture plates (Falcon Primaria) at 600000 viable cells per well in Dulbecco's Modified Eagles Medium (DMEM, Gibco BRL) containing 10% foetal calf serum (FCS), 10% penicillin/streptomycin (Gibco BRL)

and 10% non-essential amino acids (NEAA, Gibco BRL). After 4 hours incubation at 37°C in 5% CO_2, the medium was replaced with Minimum Essential Medium (MEM, Gibco BRL) containing NEAA and penicillin/streptomycin as above in addition to 10nM dexamethasone and 10nM insulin.

The following day cells were washed with phosphate buffered saline (PBS) and medium replaced with 1ml HEPES-buffered Krebs solution (25mM HEPES, 0.15M sodium chloride, 25 mM sodium hydrogen carbonate, 5mM potassium chloride, 2mM calcium chloride, 1mM magnesium sulphate, 1 mM potassium dihydrogen phosphate) containing the compound to be tested at the required concentration in 0.1% DMSO. Control wells contained 0.1% DMSO only and a maximum response was determined using a 10 μM treatment of a known active compound. After a preincubation period of 40 minutes at 37°C in 5% CO_2, cells were pulsed with sodium pyruvate to a final concentration of 0.5mM (containing 1-^{14}C sodium pyruvate (Amersham product CFA85) 0.18Ci/mmole) for 12 minutes. The medium was then removed and transferred to a tube which was immediately sealed with a bung containing a suspended centre well. Absorbent within the centre well was saturated with 50% phenylethylamine, and CO_2 in the medium released by the addition of 0.2μl 60% (w/v) perchloric acid (PCA). Released $^{14}CO_2$ trapped in the absorbent was determined by liquid scintillation counting. The ED_{50} for a test compound was determined in the usual way using results from 7 concentrations of the compound.

(c) In vivo elevation of PDH activity

The capacity of compounds to increase the activity of PDH in relevant tissues of rats may be measured using the test described hereinafter. Typically an increase in the proportion of PDH in its active, nonphosphorylated form may be detected in muscle, heart, liver and adipose tissue after a single administration of an active compound. This may be expected to lead to a decrease in blood glucose after repeated administration of the compound. For example a single administration of DCA, a compound known to activate PDH by inhibition of PDH kinase (Whitehouse, Cooper and Randle (1974) Biochem. J. 141, 761-774) 150 mg/kg, intraperitoneally, increased the proportion of PDH in its active form (Vary et al. (1988) Circ. Shock 24, 3-18) and after repeated administration resulted in a significant decrease in plasma glucose (Evans and Stacpoole (1982) Biochem. Pharmacol.31, 1295-1300).

Groups of rats (weight range 140-180g) are treated with a single dose or multiple doses of the compound of interest by oral gavage in an appropriate vehicle. A control group of rats is treated with vehicle only. At a fixed time after the final administration of compound, animals are terminally anaesthetised, tissues are removed and frozen in liquid nitrogen. For determination of PDH activity, muscle samples are disrupted under liquid nitrogen prior to homogenisation by one thirty-second burst in a Polytron homogenizer in 4 volumes of a buffer containing 40 mM potassium phosphate pH 7.0, 5 mM EDTA, 2mM DTT, 1% Triton X-100, 10mM sodium pyruvate, 10μM phenylmethylsulphonyl chloride (PMSF) and2μg/ml each of leupeptin, pepstain A and aprotinin. Extracts are centrifuged before assay. A portion of the extract is treated with PDH phosphatase prepared from pig hearts by the method of Siess and Wieland (Eur. J. Biochem (1972) 26, 96): 20 μl extract, 40 μl phosphatase (1:20 dilution), in a final volume of 125 μl containing 25 mM magnesium chloride, 1 mM calcium chloride. The activity of the untreated sample is compared with the activity of the dephosphorylated extract thus prepared. PDH activity is assayed by the method of Stansbie et al., (Biochem. J. (1976) 154, 225). 50 μl Extract is incubated with 0.75 mM NAD, 0.2 mM CoA, 1.5 mM thiamine pyrophosphate (TPP) and 1.5mM sodium pyruvate in the presence of 20 μg/ml p-(p-amino-phenylazo) benzene sulphonic acid (AABS) and 50 mU/ml arylamine transferase (AAT) in a buffer containing 100 mM tris(hydroxymethyl)aminomethane, 0.5 mM EDTA, 50mM sodium fluoride, 5mM 2-mercaptoethanol and 1mM magnesium chloride pH 7.8. AAT is prepared from pigeon livers by the method of Tabor et al. (J. Biol. Chem. (1953) 204, 127). The rate of acetyl CoA formation is determined by the rate of reduction of AABS which is indicated by a decrease in optical density at 460 nm.

Liver samples are prepared by an essentially similar method, except that sodium pyruvate is excluded from the extraction buffer and added to the phosphatase incubation to a final concentration of 5mM.

Treatment of an animal with an active compound results in an increase in the activity of PDH complex in tissues. This is indicated by an increase in the amount of active PDH (determined by the activity of untreated extract as a percentage of the total PDH activity in the same extract after treatment with phosphatase).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) as defined hereinbefore or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) or (I') as defined hereinbefore or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square metre body area of the animal, i.e. approximately 0.1-100 mg/kg. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention elevate PDH activity and are therefore of interest for their blood glucose-lowering effects.

A further feature of the present invention is a compound of formula (I) and pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof for use as a medicament.

According to a further feature of the invention there is provided a method for producing an elevation of PDH activity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of

formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore.

For the avoidance of doubt, aspects of the invention which relate to the use of compounds of formula (I) also relate to compounds of formula (I').

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The elevation of PDH activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

i) insulin;

ii) insulin secretagogue agents designed to stimulate insulin secretion (for example glibenclamide, tolbutamide, other sulphonylureas);

iii) oral hypoglycaemic agents such as metformin, thiazolidinediones;

iv) agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

v) agents designed to treat complications of prolonged hyperglycaemia;

vi) other agents used to treat lactic acidaemia;

vii) inhibitors of fatty acid oxidation;

viii) lipid lowering agents;

ix) agents used to treat coronary heart disease and peripheral vascular disease such as aspirin, pentoxifylline, cilostazol; and/or

x) thiamine.

As stated above the compounds defined in the present invention are of interest for their ability to elevate the activity of PDH. Such compounds of the invention may therefore be useful in a range of disease states including diabetes mellitus, peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, muscle weakness, hyperlipidaemias, Alzheimers disease and/or atherosclerosis.

In addition to their use in therapeutic medicine, the compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of elevators of PDH activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;

(vii) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in

parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent; coupling constants (J) are given in Hz; Ar designates an aromatic proton when such an assignment is made;

(ix) chemical symbols have their usual meanings; SI units and symbols are used;

(x) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(xi) solvent ratios are given in volume : volume (v/v) terms; and

(xii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); values for m/z are given; generally, only ions which indicate the parent mass are reported.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent; coupling constants (J)

are given in Hz; Ar designates an aromatic proton when such an assignment is made;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(x) solvent ratios are given in volume : volume (v/v) terms;

(xi) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); values for m/z are given; generally, only ions which indicate the parent mass are reported; and

(xii) The following abbreviations are used:

EA	elemental analysis;
DMF	*N,N*-dimethylformamide;
EtOAc	ethyl acetate;
DMA	*N,N*-dimethylacetamide; and
DCM	dichloromethane.

Example 1

3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(piperidin-1-ylsulphonyl)phenyl]propanamide.

A solution of 3,3,3-trifluoro-*N*-[4-(fluorosulphonyl)phenyl]-2-hydroxy-2-methylpropanamide (Method 1) (0.2 g), piperidine (0.1 g) and 4-dimethylaminopyridine (5 mg) in dry acetonitrile (4 ml) was heated at reflux for 3 hours. After cooling to 22°C, the reaction mixture was diluted with water (30 ml) and extracted with EtOAc (3 x 15 ml). The combined organic extracts were washed with 1M HCl, brine, dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Recrystallization from methyl-*t*-butylether/hexane gave the title compound as a colourless crystalline solid, (0.2 g). Mp 164-166°C; MS: 381 $(M+H)^+$; NMR: (250 MHz, $CDCl_3$): 1.42 (m, 2H), 1.64 (m, 4H), 1.77 (s, 3H), 2.97 (t, 4H), 3.79 (s, 1H), 7.73 (s, 4H), 8.67 (s, 1H); EA for $C_{15}H_{19}F_3N_2O_4S$: Calculated: C, 47.36; H, 5.03; N, 7.37. Found: C, 47.38; H, 5.16; N, 7.30.

Examples 2-3

Following the procedure of Example 1 and using the appropriate starting material the following compounds were prepared.

Ex	Compound	NMR	MS $(M-H)^+$
2 [1]	3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholino-sulphonyl)phenyl]propanamide	1.59 (s, 3H), 2.81-2.85 (m, 4H), 3.60-3.63 (m, 4H), 7.58 (s, 1H), 7.66-7.71 (m, 2H), 8.04-8.08 (m, 2H), 10.45 (s, 1H)	383
3 [2]	3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholino-sulphonyl)phenyl]propanamide	1.60 (s, 3H), 2.64-2.68 (m, 4H), 3.16-3.20 (m, 4H), 7.58 (s, 1H), 7.69-7.72 (m, 2H), 8.03-8.07 (m, 2H), 10.43 (s, 1H)	399

[1] The crude reaction product was purified by chromatography (6:1 DCM : EtOAc).

[2] The crude reaction product was recrystallized from methyl-*t*-butyl ether/hexane.

Example 4

3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(pyrrolidin-1-ylsulphonyl)phenyl]propanamide.

A solution of 3,3,3-trifluoro-*N*-(4-flurosulphonylphenyl)-2-hydroxy-2-methylpropanamide (Method 1) (0.25 g), pyrrolidine (0.28 g), and 4-pyrrolidinopyridine (12 mg) in dry acetonitrile (3 ml) was heated at reflux for 24 hours. After cooling to 22°C, the reaction mixture was diluted with water (25 ml) and extracted with EtOAc (3 x 15 ml). The combined organic extracts were washed with 1M HCl, brine, dried (Na_2SO_4) and evaporated to give an oil which crystallised upon suspension in hexane to yield the title compound as an off-white crystalline solid (0.27 g). Mp 183-186°C; MS: 367$(M+H)^+$; NMR: 1.59 (s, 3H), 1.62 (m, 4H), 3.12 (m, 4H), 7.56 (s, 1H), 7.75-7.77 (m, 2H), 8.00-8.03 (m, 2H), 10.40 (s, 1H); EA for $C_{14}H_{17}F_3N_2O_4S$: Calculated: C, 45.89; H, 4.68; N, 7.65; Found: C, 45.98; H, 4.76; N, 7.56.

Example 5

N-[4-(*N*,*N*-Dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide.

A solution of 3,3,3-trifluoro-*N*-[4-(fluorosulphonyl)phenyl]-2-hydroxy-2-methylpropanamide (Method 1) (0.2 g), di-*N*-propylamine (0.25 g) and 4-dimethylaminopyridine (13.0 mg) in dry acetonitrile (3 ml) was heated at reflux for 4 days. The reaction mixture was cooled to 22°C, diluted with water (30 ml) and extracted with EtOAc (2 x 15 ml). The combined EtOAc extracts were washed with 1M HCl, brine, dried and evaporated to give an oil. The oil was purified by chromatography (12:1; $CHCl_3$: diethyl ether) to yield an oil which crystallised from hexane to produce the title compound as a colourless crystalline solid (87.5 mg). Mp 132-134°C; MS: 397 $(M+H)^+$; NMR (250M Hz): 0.77-0.83 (t, 6H), 1.41-1.49 (m, 4H), 1.58 (s, 3H), 2.96-3.02 (t, 4H), 7.54 (s, 1H), 7.72-7.75 (m, 2H), 7.96-7.98 (m, 2H), 10.36 (s, 1H) EA for $C_{16}H_{23}F_3N_2O_4S$: Calculated: C, 48.47; H, 5.85; N, 7.07; Found: C, 48.84; H, 5.90; N, 6.89.

Example 6

N-[4-(*N*,*N*-Dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide.

To a cooled (-10°C) solution of α-trifluoromethyl lactic acid (0.69 g) in dry DMA (5 ml) was added thionyl chloride (0.33 ml) dropwise over 2 mins. The mixture was stirred at -10°C for 90 mins, then treated successively with 4-pyrrolidinopyridine (13 mg), di-isopropylethylamine (0.76 ml), and 4-(*N*,*N*-dimethylaminosulphonyl)aniline (Method 2) (0.88 g). The reaction mixture was stirred at 22°C for 48 hours, then diluted with water and extracted with EtOAc. The combined EtOAc extracts were washed with 1M HCl, brine, dried and the solvent evaporated. The crude product was purified by chromatography (12:1 DCM: EtOAc) and recrystallized from methyl-*t*-butyl ether/hexane to give the title compound as a colourless crystalline solid (0.56 g). Mp 139-141°C; MS: 341 $(M+H)^+$; NMR (250 MHz): 1.60 (s, 3H), 2.58 (s, 6H), 7.58 (s, 1H), 7.69-7.73 (d, 2H), 8.03-8.06 (d, 2H); EA for $C_{12}H_{15}F_3N_2O_4S$: Calculated: C, 42.35; H, 4.44; N, 8.23; Found: C, 42.21; H, 4.54; N, 8.15.

Examples 7-8

Following the procedure of Example 6 and using the appropriate starting material the following compounds were prepared.

Ex	Compound	EA	MS $(M-H)^+$	SM
7	3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylamino-sulphonyl)phenyl]propanamide.	$C_{16}H_{15}F_3N_2O_4S$: Calculated: C, 49.48; H, 3.89; N, 7.21; Found: C, 49.51: H, 3.89; N, 7.18.	389	Meth 3
8	*N*-[4-(*N*,*N*-Diphenylamino-sulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	$C_{22}H_{19}F_3N_2O_4S$: Calculated: C, 56.89; H, 4.12; N, 6.03. Found: C, 56.92; H, 4.25; N, 5.96	465	Meth 4

Example 9

N-[4-(Aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide.

To a cooled (-20°C) solution of α-trifluoromethylacetic acid (0.2 g) in dry DMA (4 ml) was added thionyl chloride (0.16 g) in one portion. The mixture was stirred for 15 mins, warmed to -5°C over 45 mins, then treated with sulphanilamide (0.21 g). The mixture was warmed to 22°C and stirred for 6 hours, then diluted with water (40 ml) and extracted with EtOAc (4 x 15 ml). The organic extracts were combined and washed with brine, dried, and concentrated *in vacuo* to give an oil. Purification by chromatography (2:1 EtOAc: hexane) and recrystallization from methyl-*t*-butyl ether/hexane gave the title compound as a pale yellow crystalline solid (0.17 g). Mp 179-182°C; MS: 313 $(M+H)^+$; NMR (250MHz): 1.58 (s, 3H), 7.29 (s, 2H), 7.54 (s, 1H), 7.74-7.77 (m, 2H), 7.89-7.93 (m, 2H), 10.28 (s, 1H); EA for $C_{10}H_{11}F_3N_2O_4S$: Calculated: C, 38.46; H, 3.55; N, 8.97; Found: C, 38.34; H, 3.51; N, 8.89.

Example 10

N-[4-(*N*,*N*-Diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide.

To a solution of α-trifluoromethyl lactic acid (0.37 g) in dry tetrahydrofuran (10 ml) at 22°C was added carbonyldiimidazole (0.38 g) in one portion. The mixture was stirred for 30 mins, then treated with 4-(*N*,*N*-diethylaminosulphonyl)aniline (Method 5) (0.53 g) and stirred at 22°C for 1 hour followed by heating at reflux for 18 hours. After cooling to 22 °C, the mixture

was concentrated to an oil which was purified by chromatography (9:1 DCM: diethyl ether) and crystallisation from hexane to produce the title compound as a colourless crystalline solid (0.15 g). Mp 115-130°C; MS: 341 $(M+H)^+$; NMR (250MHz, $CDCl_3$): 1.12 (t, 6H), 1.78 (s, 3H), 3.22 (s, 4H), 3.73 (s, 1H), 7.67-7.79 (m, 4H), 8.62 (brs, 1H); EA for $C_{14}H_{19}F_3N_2O_4S$: Calculated: C, 45.64; H, 5.19; N, 7.61; Found: C, 45.74; H, 5.22; N, 7.66.

Example 11

3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl] propanamide.

To a cooled (-20°C) solution of α-trifluoromethyl lactic acid 0.20 g in dry DMA (4 ml) was added thionyl chloride (0.16 g). The reaction mixture was stirred for 1 hour, then warmed to 0°C over 30 mins and treated with 4-(*N*-phenyl-*N*-methyl-aminosulphonyl)aniline (Method 6) (0.34 g). After stirring at 22°C for 24 hours, the reaction mixture was diluted with water (30 ml) and extracted with EtOAc (2 x 20 ml). The combined EtOAc extracts were washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure to give an oil which was purified by chromatography (1:1 hexane: EtOAc) and recrystallized from methyl-*t*-butyl ether/hexane to produce the title compound as a colourless solid (0.31 g). Mp 147-149°C; MS: 403 $(M+H)^+$; NMR (250 MHz): 1.55 (s, 3H), 3.09 (s, 3H), 7.05-7.08 (m, 2H), 7.28-7.43 (m, 5H), 7.53 (s, 1H), 7.91-7.95 (m, 2H), 10.36 (brs, 1H); EA for $C_{17}H_{17}F_3N_2O_4S$: Calculated: C, 50.78; H, 4.26; N, 6.97; Found: C, 50.80; H, 4.37; N, 6.93.

Example 12

R-*N*-[2-Methyl-4-(*N*-ethylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide

A solution of S-3,3,3-trifluoro-2-hydroxy-2-methylpropanoylchloride (Method 10) (200 mg, 1.1 mmol) in DCM (4 ml) was added to a stirred mixture of 2-methyl-4-(*N*-ethylanilinosulphonyl)aniline (Method A) (350 mg, 1.1mmol) and 2, 6-di-*t*-butylpyridine (0.3 ml, 1.3mmol) in DCM (10 ml). The resultant mixture was stirred at ambient temperature overnight and then concentrated. The residue was purified by column chromatography using 10% EtOAc in DCM to yield the title compound as a foam (103 mg, 0.22mmol). MS: 429.

Examples 13-16

The procedure described in Example 12 was repeated using the appropriate 4-aminobenzenesulphonamide to replace the 2-methyl-4-(*N*-ethylanilinosulphonyl)aniline to obtain the compounds described below. "Meth" refers to the Method (see section on Starting Materials below) used to make said appropriate sulphonamide.

Ex	Compound	MS	Meth
13[1]	R-*N*-[2-Methyl-4-(morpholinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	395	7
14	R-*N*-[2-Methyl-4-(*N*-methylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methyl-propanamide	415	7
15	R-*N*-[2-Methyl-4-(4-methoxy-*N*-methylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	445	7
16	R-*N*-[2-Methyl-4-(2-chloro-5-methylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	449	7

[1] NMR ($CDCl_3$): 1.7 (s, 3H), 2.3 (s, 3H), 2.8-3.0 (m, 4H), 3.6 (s, 1H), 3.6-3.8 (m, 4H), 7.5 (s, 1H), 7.5-7.6 (m, 1H), 8.3 (d, 1H), 8.5 (s, 1H)

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method 1

3,3,3-Trifluoro-*N*-[4-(fluorosulphonyl)phenyl]-2-hydroxy-2-methylpropanamide

To a cooled (-20°C) solution of α-trifluoromethyl lactic acid (2.0 g) in dry DMA (15 ml) was added thionyl chloride (0.97 ml) dropwise over 10 mins. The reaction mixture was stirred at -

20°C for 1 hour, warmed to 0°C over 1 hour, then treated with sulphanilyl fluoride (2.22 g) in one portion and heated at 100°C for 24 hours. After cooling to 22°C the reaction mixture was diluted with water (150ml) and extracted with EtOAc (3 x 35 ml). The combined organic extracts were washed with water, brine, dried and the solvent removed under reduced pressure. The crude product was purified by chromatography (13:1; DCM:Et_2O) and recrystallized from methyl-*t*-butyl ether to give the title compound as colourless crystals, (1.7 g). Mp 152-154°C; MS: 316 $(M+H)^+$; NMR ($CDCl_3$): 1.78 (s, 3H), 3.51 (brs, 1H), 7.86-7.89 (m, 2H), 7.99-8.03 (m, 2H), 8.79 (brs, 1H). EA: $C_{10}H_9F_4NO_4S$: Calculated: C, 38.10; H, 2.88; N, 4.44; Found: C, 38.21; H, 2.97; N, 4.44.

Method 2

4-(*N*,*N*-Dimethylaminosulphonyl)aniline

To a suspension of *p*-acetamidobenzenesulphonyl chloride (2.0 g) in dry acetonitrile (15 ml) at 22°C was added 40% aqueous dimethylamine (30 ml), and the mixture was stirred for 18 hours. The reaction mixture was concentrated and partitioned between EtOAc and water. The EtOAc was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a colourless crystalline solid (1.17 g). This was dissolved in ethanol and the resultant solution was treated with concentrated hydrochloric acid and heated to reflux. The reaction mixture was then cooled to 22°C and adjusted to pH 8 with concentrated NH_4OH. The resultant suspension was cooled, filtered, the solvent washed with water and dried to give a light tan solid (0.88 g); MS: 201 $(M+H)^+$; NMR: 2.50 (s, 6H), 6.04 (brs, 2H), 6.65 (d, 2H), 7.35 (d, 2H).

Methods 3-4

Following the procedure of Method 2 and using the appropriate starting material the following compounds were prepared.

Meth	Compound
3	4-(*N*-Phenylaminosulphonyl)aniline
4	4-(*N*,*N*-Diphenylaminosulphonyl)aniline

Method 5

4-(*N*,*N*-Diethylaminosulphonyl)aniline

A mixture of sulphanilic acid (2.0 g) and phosphorous pentachloride (5.97 g) was heated to 140°C, the resulting melt stirred for 10 mins, then treated cautiously with phosphorous oxychloride (50 ml) and heated at reflux for 3 hours. After cooling to 22°C, the reaction mixture was carefully poured onto ice (600 g) and vigorously stirred for 30 mins. The suspension was filtered and the solid washed with water and dried to give 2.3 g of hydroscopic intermediate *N*-(4-chlorosulphonylphenyl)phosphoramidyl dichloride. A solution of the phosphoramidyl dichloride (1.2 g) in diethyl ether (35 ml) was treated with diethylamine (5.17 ml) and the resulting suspension heated at reflux for 48 hours. After evaporation of diethyl ether at reduced pressure, the pale white solid was treated with concentrated hydrochloric acid (60 ml) and heated at reflux for 8 hours. Upon cooling to 0°C and adjustment to pH 8 with concentrated ammonium hydroxide, the solid suspension was filtered, washed with water and dried to give the title compound as a colourless crystalline solid (0.54 g); MS: 229 $(M+H)^+$; NMR ($CDCl_3$): 1.11 (t, 6H), 3.19 (q, 4H), 4.08 (brs, 2H), 6.65-6.68 (m, 2H), 7.56-7.59 (m, 2H).

Method 6

4-(*N*-Phenyl-*N*-methylaminosulphonyl)aniline

A suspension of *N*-(4-chlorosulphonylphenyl)phosphoramidc dichloride (1.0 g) and *N*-methylaniline (2.49 g) in water (5 ml) was heated at reflux for 18 hours. After cooling to 0 °C and adjustment to pH2 with concentrated hydrochloric acid, the suspension was heated at reflux for 30 mins, then cooled to 0°C and adjusted to pH 8 with concentrated ammonium hydroxide. The suspension was extracted with EtOAc (3 x 40 ml), the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to an oil. Purification by chromatography (3:2 hexane: EtOAc) gave the title compound as a colourless crystalline solid (0.65 g); MS: 263 $(M+H)^+$; NMR ($CDCl_3$): 3.13 (s, 3H), 4.11 (brs, 2H), 6.58-6.62 (m, 2H), 7.10-7.13 (m, 2H), 7.23-7.31 (m, 5H).

Method 7

2-Methyl-4-(*N*-ethylanilinosulphonyl)aniline

A solution of *N*-acyl-2-methyl-4-chlorosulphonylaniline (Method 8) (500 mg, 2 mmol), *N*-ethylaniline (240 mg, 2 mmol) and pyridine (0.18 ml, 2.2 mmol) in DCM (10 ml) was stirred at ambient temperature for 15h. The solution was washed with 1M aqueous hydrochloric acid and brine, dried and evaporated to dryness. The residue was dissolved in ethanol (10 ml) and 2M aqueous sodium hydroxide (5 ml) was added. The mixture heated at 70°C for 22h and then cooled to ambient temperature and evaporated to dryness. Water (25 ml) was added to the residue and the solution was neutralised to pH 7.0 by addition of 1M aqueous hydrochloric acid. The aqueous solution was extracted with EtOAc, the EtOAc extracts were washed with brine, dried and evaporated to dryness to yield the title compound (360 mg, 1.2 mmol). MS: 289.

Method 8

N-Acyl-2-methyl-4-chlorosulphonylaniline

N-Acyl-2-methyl-4-sulphoaniline triethylamine salt (1:1) (Method 9) (35 g, 0.11 mol) was added portion-wise, over 30mins, to $POCl_3$ (50 ml) at 0°C. The reaction mixture was stirred at room temperature for 15h and then poured slowly onto a stirred solution of ice-water. After stirring for 15mins the mixture was filtered to yield the title compound as a solid (25 g, 0.10 mol). MS: 246.

Method 9

N-Acyl-2-methyl-4-sulphoaniline triethylamine salt (1:1)

2-Methyl-4-sulphoaniline (30 g, 0.16 mol) was dissolved in acetic anhydride (50 ml) and stirred in an ice bath. Triethylamine (23 ml, 0.18 mol) was added very slowly with vigorous stirring (and concomitant release of heat). The reaction mixture was left to stir for 14h, at which point a solid formed; this was filtered to yield the title compound (35 g, 0.11 mol). NMR: ($CDCl_3$): 1.2 (t, 9H), 2.1 (s, 3H), 2.2 (s, 3H), 3.0 (q, 6H), 7.2-7.6 (m, 3H), 8.2 (brs, 1H); MS: 228.

Method 10

S-3,3,3-Trifluoro-2-hydroxy-2-methylpropanoyl chloride

Oxalyl chloride (1.07 ml, 12 mmol) was added dropwise to a stirred suspension of (R)-(+)-2-hydroxy-2-methyl-3,3,3-trifluoropropanoic acid (Method 11) (1.95 g, 12 mmol) in DCM (42 ml) and DMF (0.8 ml). The mixture was stirred at ambient temperature for 2-15h to yield a solution of the title compound which was used in subsequent reactions without further purification.

Method 11

(R)-(+)-2-Hydroxy-2-methyl-3,3,3-trifluoropropanoic acid

R/S-2-Hydroxy-2-methyl-3,3,3-trifluoropropanoic acid was resolved according to the resolution method described in European Patent Application No. EP 524781 (described for the preparation of the (S)-(-) acid) except that (1S, 2R)-norephedrine was used in place of (1R, 2S)-norephedrine or (S)-(-)-1-phenylethylamine to yield the title compound, $[\alpha]_D^{20}$ +18.1° (*c*, 8.8 in MeOH); NMR analysis of the acid in the presence of (R)-(+)-1-phenylethylamine gave an enantiomerical purity of >98%. NMR ($CDCl_3$): 1.27 (s, 3H) for the (R)-enantiomer, 1.21 (s, 3H) for the (S)-enantiomer.

Example 17

The following illustrate representative pharmaceutical dosage forms containing the compound of formula **(I)**, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur.	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur.	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur.	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur.	488.5
	Magnesium stearate	1.5

(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	1M Sodium hydroxide solution	15.0% v/v
	0.1M Hydrochloric acid	(to adjust pH to 7.6)
	Polyethylene glycol 400	4.5% w/v
	Water for injection to 100%	

(f)	Injection II	10 mg/ml)
	Compound X	1.0% w/v
	Sodium phosphate BP	3.6% w/v
	0.1M Sodium hydroxide solution	15.0% v/v
	Water for injection to 100%	

(g)	Injection III	(1mg/ml.buffered to pH6)
	Compound X	0.1% w/v
	Sodium phosphate BP	2.26% w/v
	Citric acid	0.38% w/v
	Polyethylene glycol 400	3.5% w/v
	Water for injection to 100%	

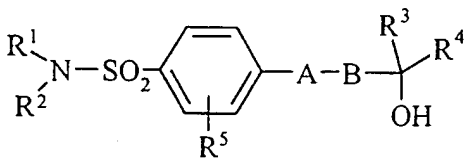
Note:

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS:

What is claimed is:

1. The use of a compound of the formula **(I)**:



(I)

wherein:

either $\mathbf{R^1}$ and $\mathbf{R^2}$ are each selected independently from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is unsubstituted or substituted by one or two substituents selected independently from C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, hydroxy, halo and cyano,

or R^1 and R^2 together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl, pyrrolidinyl or imidazolyl;

A-B is selected from NHCO, OCH_2, SCH_2, $NHCH_2$, *trans*-vinylene and ethynylene;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are independently C_{1-3}alkyl substituted by from 0 to 2k+1 atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said C_{1-3}alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4, together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to 2m-2 fluorine atoms wherein m is the number of carbon atoms in said ring; and

$\mathbf{R^5}$ is hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano, nitro, C_{2-4}alkenyloxy or trifluoromethylthio;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the elevation of PDH activity in warm-blooded animals such as humans.

2. The use of a compound of the formula **(I)** as claimed in claim 1 wherein R^1 and R^2 are each independently selected from hydrogen, C_{1-3}alkyl and phenyl which is optionally substituted by one or two substituents selected from methoxy, methyl and halo,

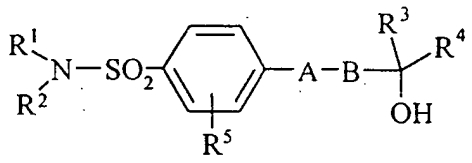
or R^1 and R^2 together with the nitrogen group to which they are attached form morpholino, thiomorpholino, piperidinyl or pyrrolidinyl.

3. The use of a compound of the formula **(I)** as claimed in claim 1 or 2 wherein one of R^2 and R^3 is methyl and the other is trifluoromethyl.

4. The use of a compound of the formula **(I)** as claimed in claim 1, 2 or 3 wherein R^5 is methyl.

5. The use of a compound of the formula **(I)** as claimed in claim 1, 2, 3 or 4 wherein A-B -NHCO-.

6. A compound of the formula **(I)**:



(I)

wherein ring R^1, R^2, R^3, R^4, R^5 and A-B are as defined in claim 1:

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof provided said compound is not:

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-piperidinylsulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(1-pyrrolidinylsulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(morpholinosulphonyl)phenyl]propanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(thiomorpholinosulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-dipropylaminosulphonyl)phenyl]-3,3,3-trifluro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-dimethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(aminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

N-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenyl-*N*-methylaminosulphonyl)phenyl] propanamide;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinylsulphonyl)phenyl]but-1-yne;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(1-pyrrolidinylsulphonyl)phenyl]-trans-but-1-ene;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-methyl-*N*-phenylaminosulphonyl)phenyl]but-1-yne;

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(*N*-Methyl-*N*-phenylaminosulphonyl)phenyl]-trans-but-1-ene;

1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methylbut-1-yne;

1-[4-(*N*,*N*-diethylaminosulphonyl)phenyl]-4,4,4-trifluoro-3-hydroxy-3-methyl-trans-but-1-ene;

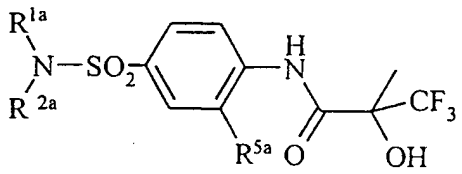
3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-[4-(*N*-phenylaminosulphonyl)phenyl]propanamide;

N-[4-(*N*,*N*-diphenylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide; or

4,4,4-trifluoro-3-hydroxy-3-methyl-1-[4-(morpholinosulphonyl)phenyl]-trans-but-1-ene;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

7. A compound of the formula **(I')**:



(I')

wherein:

R^{1a} and R^{2a} are each selected independently from hydrogen, C_{1-3}alkyl, pyridyl and phenyl which is unsubstituted or substituted by one or two substituents selected independently from C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, hydroxy, halo and cyano,

or R^{1a} and R^{2a} together with the nitrogen atom to which they are attached form morpholino, thiomorpholino, piperidinyl, pyrrolidinyl or imidazolyl; and

R^{5a} is C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano, nitro, C_{2-4}alkenyloxy or trifluoromethylthio;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8. A compound of formula **(I)** or **(I')** as claimed in claim 6 or 7 which is selected from:

R-*N*-[2-Methyl-4-(*N*-ethylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

R-*N*-[2-Methyl-4-(morpholinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

R-*N*-[2-Methyl-4-(*N*-methylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methyl-propanamide;

R-*N*-[2-Methyl-4-(4-methoxy-*N*-methylanilinosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide; and

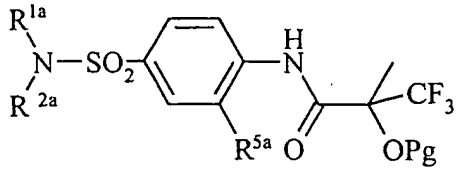
R-*N*-[2-Methyl-4-(2-chloro-5-methylaminosulphonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

9. A pharmaceutical composition which comprises a compound of the formula **(I)** or **(I')** as defined in claim 6, 7 or 8 which comprises a compound of the formula **(I)** or **(I')** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, in association with a pharmaceutically acceptable excipient or carrier.

10. A process for preparing a compound of formula **(I')** as claimed in claim 7 or 8 (in which variable groups are as defined for formula **(I')** unless otherwise stated) which comprises:

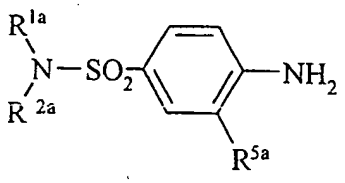
(a) deprotecting a protected compound of formula **(II)**:



(II)

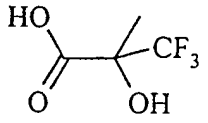
where Pg is an alcohol protecting group;

(b) coupling an aniline of formula **(III)**:



(III)

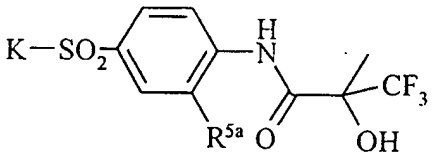
with an acid of formula **(IV)**:



(IV)

(c) coupling an aniline of formula **(III)** with an activated acid derivative of formula **(IV)**;

(d) reacting a compound of formula **(XI)**:



(XI)

where K is a leaving atom or group with an amine of formula $R^{1a}R^{2a}NH$;

and thereafter if necessary:

i) converting a compound of the formula **(I')** into another compound of the formula **(I')**;

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* cleavable ester.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB 99/01735

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/29 C07C311/46 C07D295/22 A61K31/18 A61K31/445 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 625 516 A (ZENECA LTD) 23 November 1994 (1994-11-23) cited in the application page 5, line 44 - line 49; claim 1 ---	6,9
A	OHNMACHT, CYRUS J. ET AL: "N-Aryl-3,3,3-trifluoro-2-hydroxy-2-methyl propanamides: KATP Potassium Channel Openers. Modifications on the Western Region" J. MED. CHEM. (1996), 39(23), 4592-4601 , XP002110510 --- -/--	6,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 1999	12/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01735

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EMPFIELD J R ET AL: "4-Sulfonamidoanilide tertiary carbinols: a novel series of potassium channel openers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 7, 8 April 1997 (1997-04-08), page 775-778 XP004136128 ISSN: 0960-894X	6,9
A	WO 96 28151 A (ZENECA LTD ;CONSTANTIN TEODOSIU DUMITRU (GB); TIMMONS JAMES ARCHIB) 19 September 1996 (1996-09-19) page 1	1,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/01735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0625516 A	23-11-1994	AT 170852 T	15-09-1998
		CA 2118822 A	18-11-1994
		DE 69413118 D	15-10-1998
		DE 69413118 T	11-02-1999
		ES 2121597 T	01-12-1998
		JP 6329617 A	29-11-1994
		US 5510386 A	23-04-1996
		US 5693639 A	02-12-1997
WO 9628151 A	19-09-1996	AU 4950296 A	02-10-1996
		EP 0814801 A	07-01-1998
		JP 11501653 T	09-02-1999